Cellulat

Jaime Lagunez-Otero, Pedro Pablo González Pérez, Maura Cárdenas-García,
Octavio Rosas, & Armando Franyuti
Instituto de Química, Universidad Nacional Autónoma de México
Ciudad Universitaria, 04510, MÉXICO, D.F.
ppgp@servidor.unam.mx, lagunez@servidor.unam.mx http://132.248.11.4

Abstract

In order to model the cell it is essential to understand the communication system that governs its behaviour. Though it is true that determining the kinetic equations of the biochemistry involved in vital functions is very useful, the management of the information in order for the cell to make the correct physiological decisions is even more so. This can be appreciated in the determinacy of the correct function of oncogenes coding for signal transduction components. We emulate a signal transduction network using behaviour-based systems and the blackboard architecture. Our construct, named Cellulat, allows one to observe two essential aspects of the intracellular signalling networks: (1) the apparent behavioural capabilities and (2) a spatial organization. The first user interfaces for creating a model cell are presented, the ontology used, as well as a simple example for the analysis of a kinase pathway.

Introduction

Most artificial life models have centred on the ability of describing external properties such as reproduction, competition, and selection in the better cases using biochemical considerations. This has done without seriously taking into account the internal communication mechanisms required to observe the phenomena. Our thesis focuses on the idea that in order to comprehend vital properties one must understand the cellular information processing system. Our construct is composed of autonomous agents representing elements involved in signal transduction. We present here the ontology used, the behaviour based architecture, the agent design and the interfaces which permit the creation of the model.

The effect of signals received by a cell can be the alteration of the cell metabolism, its differentiation, mitosis, or apoptosis, among other biological functions. Each cell in an organism receives specific combinations of chemical signals generated by other cells. Once the signals bind to the receptors, different processes are activated generating complex networks. Paradigms that have been used to model cellular signalling networks are artificial neural networks (Bray & Lay 1994; Pritchard & Dufton 2000), Boolean networks (Edwards 1995), petri nets (Fuss 1987), rule-based systems (Cárdenas 2000), cellular automata (Edwards 1995), and multi-agent systems (Fisher, Malcom, & Paton 2000; Paton, Staniford, & Kendall 1995; Schwab & Pienta 1997).

Because we are interested in the behavioural repertoire of the cell, the theory of behaviour based systems (Brooks 1986) is proposed to constitute a better approach for its simulation. Furthermore, the communication between agents in our model takes place through a blackboard architecture (Nii 1989) in which cellular elements related to signalling pathways can be explicitly represented.

In this paper, we postulate that an effective and robust model of intracellular signalling can be obtained when the main structural and functional characteristics of behaviour-based systems and the blackboard architecture are joined.

Signalling intracellular networks and Behaviour based systems

The transfer of the external milieu signal to the nucleus can come from the binding of the given signal by the receptor. This frequently generates a diffusible intracellular second messenger by way of a series of phosphorylations and multimerization of cytoplasmic and membrane bound enzymes. Many different receptors generate the same second messenger such as cAMP, cGMP, The convergence and divergence of the independent signals makes the system very interesting from the point of view of the studies of information transfer. When the delicate balance of transduction is affected there is a risk of damaging the cellular growth control by activating the replication machinery out of time and eventually inducing a pathologic state such as a neoplasia in the neighboring cells and tissue. Considering the relevance of the phenomena and the complexity of the network, it becomes essential to use computational techniques to deal with the system.

In computer science, an autonomous agent interacts directly with its problem domain; it perceives its environment through its sensors and acts on it through its actuators. The autonomous agent tries to satisfy a set of goals or motivations in an environment that can be dynamic and complex. It decides how to relate its external and internal inputs with its actions (Maes 1994). Adaptation is one of the desirable characteristics in autonomous agents. An autonomous agent is adaptive if it has abilities that allow him to improve its performance in time. The theory of behaviour-based systems (Brooks 1986) provides a new strategy for the construction of autonomous agents, inspired by etology. The aim of behaviour-based systems (BBS) is to provide control to autonomous agents which will eventually contribute to its capacity to adapt.

A cell signalling network can be seen as an adaptive autonomous agent or as a society of adaptive autonomous agents, where each agent can exhibit a particular behaviour depending on its "cognitive" capabilities. As an autonomous agent, the network perceives its external environment through its surface receptors and acts on it by means of the generation of new signals, which will be able to affect the behaviour of other cells. The cell's external environment is also dynamic and complex, in which an extensive range of signals and combinations of these can exist. Furthermore, as in an autonomous agent, the network and in consequence the cell itself decides how to relate the received external signals (signalling molecules) to its internal signals (secondary messengers), so that their goals (differentiation, proliferation, survival, among others) can be satisfied. The cell is now able also to adapt to its environment by constantly modifying its behaviour in order to respond to the changes that take place in the environment and to the pattern of signals received.

Cellulat: a signalling network based construct

The model presented constitutes a refinement and adaptation of an action selection mechanism structured on a blackboard architecture, termed, Internal Behaviours Network (IBeNet) (Gershenson, González, & Negrete 2000; Gershenson & Negrete 2000; González 2000; González *et al.* 2000). The IBeNet was initially built to study action selection in autonomous agents such as physical robots and animats, it constitutes a working environment for the bottom-up modelling of information processing systems characterized by:

1. coordination and opportunistic integration of several tasks in real time,
2. use of several abstraction or context levels for the different types of information that participate in the processing network,
3. decision making,
4. action selection and
5. adaptation.

Although, the intracellular signalling model proposed can be seen as the assignation of a new semantic to the components of the IBeNet, we assume here that this is equivalent to the creation of correspondence of these same semantics to the components of the blackboard architecture, when the two following considerations are done:

1. knowledge sources are seen as either internal autonomous agents or interface autonomous agents and
2. the blackboard architecture control is distributed now between these two types of autonomous agents.

The blackboard architecture described in section 3 takes into account the considerations (1) and (2). In this way, it is not necessary to explain the structural and functional details of IBeNet here to understand the intracellular signalling model proposed.

Three main components define the Cellulat structure: the blackboard, the internal autonomous agents and interface autonomous agents. The blackboard represents the cell's internal medium.

The blackboard levels correspond to different cellular structures through which the signal transduction occurs. In this way, the cellular membrane, the cytosol and the nucleus are different blackboard levels. The solution elements recorded on the blackboard represent two main types of intracellular signals: secondary messenger molecules and activation/inactivation signals. Both types are synthesized or created by internal autonomous agents and these, either directly or indirectly, promote the activation/inactivation of other internal autonomous agents. The internal autonomous agents model the components of the intracellular signalling network such as proteins, enzymes and other mechanisms necessary to carry out the signal transduction. On the other hand, the interface autonomous agents model the cell surface receptors and the mechanisms for the secretion of signalling molecules. Each agent, independently of its type, has a condition part and an action part; the way in which both parts are linked depends on the complexity of the intracellular component modelled by agent. The work of both types of agents is event-directed. This is, each intracellular signal registered on the blackboard or each extracellular signal perceived constitutes an event, which could activate or inactivate one or more autonomous agents. When an internal autonomous agent is activated then this one executes consists in the synthesis or modification of a signal on the blackboard.

Modelling spatial organization

An important aspect to consider in the modelling of intracellular signalling networks is their spatial organization. Experimental data recently obtained suggest

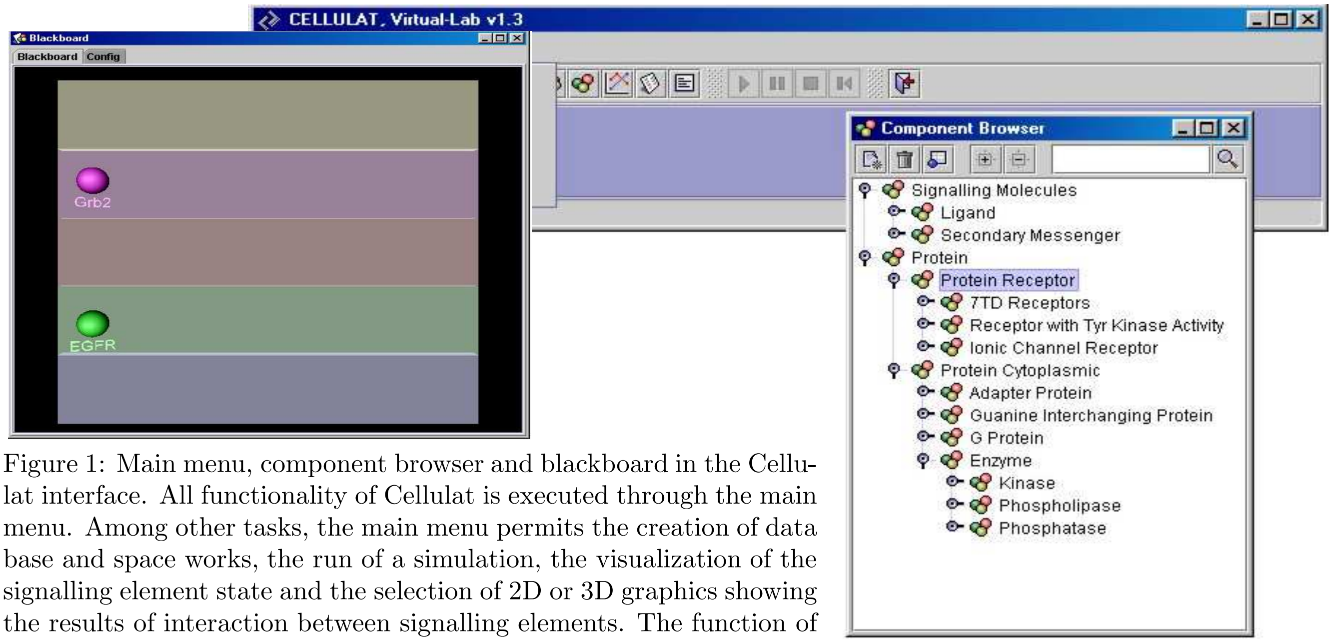

Figure 1: Main menu, component browser and blackboard in the Cellulat interface. All functionality of Cellulat is executed through the main menu. Among other tasks, the main menu permits the creation of data base and space works, the run of a simulation, the visualization of the signalling element state and the selection of 2D or 3D graphics showing the results of interaction between signalling elements. The function of the component browser is the creation, modification and visualization of the different signalling elements. The blackboard shows the characteristics of the intracellular milieu. In this case, on the compartment corresponding to the membrane a population of EGF receptors has been created, whereas on the compartment cytosol a population of adapter proteins Grb2.

clearly that many intracellular signalling networks exhibit a high level of spatial organization. Intracellular signalling models developed recently approach to this question (Fisher, Malcom, & Paton 2000). Cellulat allows modelling the spatial organization taking account two organizational criteria of the blackboard architecture. One is the horizontal organization, given by the different abstraction levels of the blackboard, which allow an intralevel signal processing. The other is the vertical organization, given by columns that cross different blackboard levels. These columns arise as result of the adjoining work of several internal autonomous agents that operate at a same section of blackboard. We have named these columns "agency columns". Convergence and divergence of agency columns can occur (González 2000).

The process of creation, modification and visualization of the signalling elements just as the process related with the activation of the pathway and visualization of the resultant interactions are all executed through the Cellulat interface. The figure shows three screens from the Cellulat graphic interface: the main menu and the component browser and the blackboard. Through the main menu the data base and work spaces are created, the simulation of the intracellular signalling is initiated or stopped and the results of the interactions between signalling elements are showed through 2D and 3D graphics. Through component browser the different signalling elements can be created, modified and visualised

Once concluded the creation of the two signalling elements, these are placed on their corresponding cellular compartments in the blackboard. The Components are incorporated into the blackboard as colour-coded rotating spheres (see Figure 1) The type of behaviour (phosphorylated, non phophorylated, activated, non activated) of these signalling elements is represented by the intensity of their colour and rotation rate during the simulation.

Conclusions

An artificial life model which takes into account the internal communication in the cell and its structure should provide a basis for a new generation of constructs which emulate biological behaviours with a mechanistically deeper basis.

In this paper we have discussed how the fusion of the behaviour-based systems theory and the blackboard architecture constitutes a suitable approach for the modelling of intracellular signalling networks. Two basic aspects of the cellular signalling networks are of interest in Cellulat: (1) the cognitive capabilities of the signalling components, and (2) the spatial organization in the cell. This is done when considering the functional components as adaptive autonomous agents. The second aspect is targeted by the shared blackboard data structure, which allows for the modelling of spatial parameters.

In the future the present infrastructure is to permit the visualization of emergent cognitive properties of the information processing network.

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